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08/788800

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/788,800	01/22/97	BEDNAR	P0987R1

EXAMINER: GAMBEL, P

18M1/1002

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ART UNIT	PAPER NUMBER
1806	5

DATE MAILED: 10/02/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-17 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e). SEE ACTION

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES

DETAILED ACTION

1. If applicant desires priority under 35 U.S.C. 119(e) or 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant's claim to a "Serial No. To Be Assigned", filed 1/23/96, in the Oath and on the first line of the Specification is acknowledged. However, applicant has not provided the serial number of the application relied upon for priority. Therefore, at this time, the filing date of the instant application is considered to be the filing date of the instant USSN 08/788,800, that is, 1/22/97. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

In clarifying the priority date of the instant claims, applicant should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to the current priority date of 1/22/97 or to the putative priority date of 1/23/96.

2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 (see the specification at page 13, lines 9-12). However, this application fails to comply with the requirements set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is required to fulfill these requirements.

It does not appear that a sequence listing has been provided for the light chain of the full length IgG2 huH52 as disclosed on page 13, lines 9-12 of the instant specification.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. It is apparent that the H52 antibody is required to practice the claimed invention (claims 11-12). As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that if the claimed amino acid sequences of the heavy and light chain of the humanized H52 antibody are disclosed on pages 12-13 of the instant specification. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. However, if the amino acid sequences disclosed in the instant specification do not encompass the entire native H52 antibody, then applicant is required to deposit the H52 hybridoma to satisfy the deposit of biological materials under 112, first paragraph, as set forth above.

8. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOS. 8, 9, and 13-15 as salvage receptor binding epitopes, does not reasonably provide enablement for other salvage receptor binding epitopes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use other salvage receptor binding epitopes commensurate in scope with these claims. There is insufficient direction and guidance to enable one of ordinary skill in the art to make and use of the claimed anti-CD18 antibodies fused to salvage receptor binding epitopes in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size of receptor binding epitopes. An anti-CD18 antibody comprising any salvage receptor binding epitope can be any one of a number peptides or amino acid sequences, which, in turn, can read on small amino acid sequences which are incomplete regions. There is insufficient support in the specification for constructing the number of anti-CD18 antibodies comprising any or all or the myriad salvage receptor binding epitopes

which are encompassed within this language. Applicant has not enabled any salvage receptor binding epitope. One of the skill in the art would neither expect nor predict the appropriate functioning of a salvage receptor binding epitope to enhance the half-life of antibodies as broadly as is claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement. Without such guidance, the changes which can be made in the polypeptide's structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

It is suggested that LFA-1-specific antibodies and SEQ ID NOS. be explicitly recited within the claim in order to obviate these rejections.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

It is noted that "has the sequence" and having the sequence" are considered closed language phrases, the same as "consisting of".

9. Claims 11-13 and 15-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 11-12 are indefinite in the recitation of "H52" because its characteristics are not known. The use of "humanized H52 antibody" as the sole means of identifying the claimed antibody renders the claim indefinite because this is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct antibodies or cell lines.

Applicant should amend the claim to recite the SEQ ID NOS. of the humanized H52 antibody. As pointed out above in section , applicant is invited to clarify whether the humanized H52 antibody has sequences not disclosed in the specification. If the sequence of the entire H52 immunoglobulin is not disclosed and recited in the claims, then the appropriate deposit information (i.e. accession number) would obviate this rejection.

B) Claims 13 is indefinite in the recitation of a salvage receptor binding epitope because its characteristics are ambiguous and ill-defined. For example, an epitope refers to sequential and conformational antigenic determinants and a salvage receptor does not have a clear defined meaning in the art.

C) Claims 15-17 are indefinite in the recitation of "antagonist anti-CD18 antibody" because it is not clear what is being antagonized, that is, thee claims fails to state the antagonistic function which is to be achieved.

D) Claim 10 is objected to because "mins" should be recited as "minutes" for clarity.

E) The amendments must be supported by the specification so as not to add any new matter.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mori et al. (Stroke, 1992). Mori et al. teach inhibiting focal cerebral ischemia in baboons with the anti-CD18 antibody IB4 (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

13. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Clark et al. (Stroke, 1991). Clark et al. teach reducing central nervous systemic ischemic injury in rabbits with anti-CD18 antibodies (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

14. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bednar et al. (Neurol. Res., 1996). Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

15. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bednar et al. (Neurol. Res., 1996). Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

16. Claims are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients.

Mori et al. teach inhibiting focal cerebral ischemia in baboons with the anti-CD18 antibody IB4 (see entire document).

Clark et al. teach reducing central nervous systemic ischemic injury in rabbits with anti-CD18 antibodies (see entire document).

Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document).

Lindsberg et al. teach the ability of the anti-CD18 antibody given after the onset of reperfusion to treat a spinal-cord ischemia-reperfusion injury in rabbits (see entire document).

Mori et al., Clark et al., Bednar et al., Lindsberg et al. differ from the instant methods by not employing antibody fragments or humanized antibodies or treating human patients, however such antibody modifications were standard procedures in increasing therapeutic efficacy and in treating human patients at the time the invention was made.

Mori et al., Clark et al., Bednar et al., Lindsberg et al. differ from the instant methods by not teaching the particular claimed time frames of 45 minutes to 5 hours and 15 minutes to about 20 hours, however the references do teach treating within these time frames. In addition, such time frames as well as providing bolus/continuous infusion would have obvious to the ordinary artisan at the time the invention was made in providing sufficient anti-CD18 antibody depending on the need of the patient.

Claims 15-17, drawn to articles or manufacture and kits would have been obvious at the time invention was made in providing anti-CD18 antibodies in a form including the instructions for its use intended for the treatment of ischemic stroke, as taught by the references above. It was well known convention in the art to place components in a kit for convenience and economy.

One of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 1-10 and 15-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 15-17 above and in further evidence of Kim et al. (J. Neurological Sciences, 1995) as it applies to instant methods treating humans.

Kim et al. Provide evidence that CD11a and CD18 are unregulated in patient with ischemic stroke and transient ischemic attacks and that such adhesion molecules are involved in tissue injury in various cerebral vascular disorders including ischemic stroke (see entire document).

One of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 11-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 15-17 above and in further view of Hildreth et al. (Mol. Immunol., 1989) OR Hildreth (WO 9015076).

Mori et al., Clark et al., Bednar et al., Lindsberg et al., differ from the instant claims by not disclosing the H52 specificity.

Both Hildreth et al. references teach the H52 specificity. It is noted that the complete Hildreth (WO 9015076) document was not available to the examiner at this time, however it is clear that this reference teaches the use of the H52 antibody in various therapeutic modalities. Hildreth et al. (Mol. Immunol.)

Although the references are silent about the exact sequences of the H52 antibody, the recombinant techniques and computer analyses of CDR grafting known and well-practiced at the time the invention was made would have resulted in the same or very nearly the same structural and functional characteristics of the instant humanized H52 antibody and fragments thereof, since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. There appears no evidence that the instant humanized H52 antibody would differ in an unexpected or distinct manner from that available to the ordinary artisan at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select various anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke, includig the instant H52 specificity as taught by Hildreth et al.. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 13 is rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 15-17 above in view that the instant salvage receptor epitope would be derived from recombinant modeling of humanized antibodies OR in view of Presta et al. (WO 96/32478) if the instant salvage receptor epitopes are drawn to SEQ ID NOS. 8, 9, and 13-15 as salvage receptor binding epitopes.

Mori et al., Clark et al., Bednar et al., Lindsberg et al., differ from the instant claims by not disclosing salvage receptor binding epitopes.

Given the absence of clear structural limitations, the instant salvage receptor binding epitopes would read on modifications in deriving humanized antibodies including modifications to decrease immunogenicity and increase half-life via standard recombinant methods known and practiced at the time the invention was made.

Alternatively, Presta et al. teach salvage receptor epitopes to increase the half-life of antibodies, including those disclosed in the instant specification (though not claimed).

One of ordinary skill in the art at the time the invention was made would have been motivated to modify therapeutic antibodies to decrease immunogenicity and to increase half-life to increase their efficacy, including anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
September 30, 1997

Phillip Gambel